The immuno-suppressive tumor microenvironment poses a major hurdle for anti-tumor immunity and immunotherapeutic treatment approaches (Beatty, G. L., et al. Science 331 (2011) 1612-1616).

Summary ~~of the Invention~~

The present inventors have found that anti-ANG2 antibodies enhance the efficacy of CD40 agonists to treat cancers or delay progression of a tumor or the survival of a patient afflicted with cancer e.g. with a solid tumor. The delay of progression, the longer survival as well as the potential of reduced doses with lower risk of side effects represent a major benefit for patients.

Surprisingly a treatment of tumors with anti-ANG2 antibodies in combination with CD40 agonists showed strong synergistic effect on the time to tumor progression and the time of survival (whereas a combination of anti-VEGF antibodies in combination with CD40 agonists only showed small effects).

One aspect of the ~~invention~~ disclosure is an antibody that binds to human angiopoietin 2 (ANG-2) wherein the antibody is administered in combination with a CD40 agonist a) for use in treating or delaying progression of cancer, or b) for use in prolonging the survival of a patient suffering from cancer, or c) for use in stimulating an immune response or function, such as T cell activity (in one embodiment CD8 effector T cell activity) or macrophage activity (in one embodiment CD40-activated macrophage activity), or d) for use in rendering a cancer susceptible for the treatment with an antibody that binds to human angiopoietin 2 (ANG-2).

~~Another aspect of t~~The disclosure also relates to ~~invention is~~ a CD40 agonist wherein the a CD40 agonist is administered in combination with an antibody that binds to human angiopoietin 2 (ANG-2) a) for use in treating or delaying progression of cancer, or b) for use in prolonging the survival of a patient suffering from cancer, or c) for use in stimulating an immune response or function, such as T cell activity (in one embodiment CD8 effector T cell activity) or macrophage activity (in one embodiment CD40-activated macrophage activity), or d) for use in rendering a cancer susceptible for the treatment with an antibody that binds to human angiopoietin 2 (ANG-2).

~~In one aspect, t~~The ~~invention~~ disclosure also provides a method for a) treating or delaying progression of cancer, or b) prolonging the survival of a patient suffering from cancer, or c) stimulating an immune response or function, such as T cell activity (in

one embodiment CD8 effector T cell activity) or macrophage activity (in one embodiment CD40-activated macrophage activity), or d) rendering a cancer susceptible for the treatment with an antibody that binds to human angiopoietin 2 (ANG-2), wherein the method comprises the step of administering an effective amount of an anti-ANG2 antibody and an effective amount of a CD40 agonist to a patient in need thereof.

~~In another aspect, t~~The disclosure also ~~invention~~ provides the use of an anti-ANG2 antibody in the manufacture of a medicament for the treatment of cancer, wherein the antibody is for administration with a CD40 agonist.

~~Another aspect of t~~The disclosure also relates to ~~invention is~~ an antibody that binds to human angiopoietin 2 (ANG-2) in the manufacture of a medicament for
a) for use in treating or delaying progression of cancer, or
b) for use in prolonging the survival of a patient suffering from cancer, or
c) for use in stimulating an immune response or function, such as T cell activity (in one embodiment CD8 effector T cell activity) or macrophage activity (in one embodiment CD40-activated macrophage activity), or
d) for use in rendering a cancer susceptible for the treatment with an antibody that binds to human angiopoietin 2 (ANG-2);
wherein the antibody is administered with a CD40 agonist.

~~Another aspect of t~~The disclosure also relates to ~~invention is~~ a CD40 agonist in the manufacture of a medicament for
a) for use in treating or delaying progression of cancer, or
b) for use in prolonging the survival of a patient suffering from cancer, or
c) for use in stimulating an immune response or function, such as T cell activity (in one embodiment CD8 effector T cell activity) or macrophage activity (in one embodiment CD40-activated macrophage activity), or
d) for use in rendering a cancer susceptible for the treatment with an antibody that binds to human angiopoietin 2 (ANG-2);
wherein the a CD40 agonist is administered with an antibody that binds to human angiopoietin 2 (ANG-2).

~~Another aspect of t~~The ~~invention~~ disclosure also relates to ~~is~~ an antibody that binds to human angiopoietin 2 (ANG-2) in combination with a CD40 agonist a) for use in treating or delaying progression of cancer, or b) for use in prolonging the survival of a patient suffering from cancer, or c) for use in stimulating an immune response or function, such as T

cell activity (in one embodiment CD8 effector T cell activity) or macrophage activity (in one embodiment CD40-activated macrophage activity), or d) for use in rendering a cancer susceptible for the treatment with an antibody that binds to human angiopoietin 2 (ANG-2).

Another aspect of the disclosure is an antibody that binds to human angiopoietin 2 (ANG-2) wherein the antibody is administered in combination with a CD40 agonist a) for use in treating or delaying progression of cancer, b) for use in prolonging the survival of a patient suffering from cancer.

~~Another aspect of t~~The disclosure also relates to ~~invention is~~ an antibody that binds to human angiopoietin 2 (ANG-2) in combination with a CD40 agonist in the manufacture of a medicament for
a) for use in treating or delaying progression of cancer, or
b) for use in prolonging the survival of a patient suffering from cancer, or
c) for use in stimulating an immune response or function, such as T cell activity (in one embodiment CD8 effector T cell activity) or macrophage activity (in one embodiment CD40-activated macrophage activity), or
d) for use in rendering a cancer susceptible for the treatment with an antibody that binds to human angiopoietin 2 (ANG-2).

~~In one aspect, t~~The disclosure also ~~invention~~ provides a method for a) treating or delaying progression of cancer, or b) prolonging the survival of a patient suffering from cancer, or c) stimulating an immune response or function, such as T cell activity (in one embodiment CD8 effector T cell activity) or macrophage activity (in one embodiment CD40-activated macrophage activity), or d) rendering a cancer susceptible for the treatment with an antibody that binds to human angiopoietin 2 (ANG-2), wherein the method comprises the step of administering an effective amount of an anti-ANG2 antibody and an effective amount of a CD40 agonist to a patient in need thereof.

~~Another aspect of t~~The disclosure also relates to ~~invention is~~ an antibody that binds to human angiopoietin 2 (ANG-2) and a CD40 agonist for use in combination a) for treating or delaying progression of cancer, or b) for prolonging the survival of a patient suffering from cancer, or c) for stimulating an immune response or function, such as T cell activity (in one embodiment CD8 effector T cell activity) or macrophage activity (in one embodiment CD40-activated macrophage activity), or d) for rendering a cancer susceptible for the treatment with an antibody that binds to human angiopoietin 2 (ANG-2).

~~Another aspect of t~~The disclosure also relates to ~~invention is~~ an antibody that binds to human angiopoietin 2 (ANG-2) and a CD40 agonist for use in the manufacture of a medicament for

a) for treating or delaying progression of cancer, or

b) for prolonging the survival of a patient suffering from cancer, or

c) for stimulating an immune response or function, such as T cell activity (in one embodiment CD8 effector T cell activity) or macrophage activity (in one embodiment CD40-activated macrophage activity), or

d) for rendering a cancer susceptible for the treatment with an antibody that binds to human angiopoietin 2 (ANG-2).

~~Another aspect of t~~The disclosure also relates to ~~invention is~~ the use of an antibody that binds to human angiopoietin 2 (ANG-2) and a CD40 agonist in combination in the manufacture of a medicament for

a) for treating or delaying progression of cancer, or

b) for prolonging the survival of a patient suffering from cancer, or

c) for stimulating an immune response or function, such as T cell activity (in one embodiment CD8 effector T cell activity) or macrophage activity (in one embodiment CD40-activated macrophage activity), or

d) for rendering a cancer susceptible for the treatment with an antibody that binds to human angiopoietin 2 (ANG-2).

In one embodiment, the anti-ANG2 antibody is a human or humanized antibody.

Preferably, the anti-ANG2 antibody specifically binds to human ANG2 with a K_D value of less than 1.0 x 10^{-8} mol/l, as determined by surface plasmon resonance (Biacore™).

The anti-ANG2 antibody is preferably an IgG antibody and more preferably, the anti-ANG2 antibody is of human IgG1 or IgG4 subclass.

In one preferred embodiment the anti-ANG2 antibody inhibits the interaction of human ANG-2 with TIE2 receptor with an IC50 of 15 nM or less.

In one embodiment the CD40 agonist is an agonistic CD40 antibody or an agonistic CD40L polypeptide.

In one preferred embodiment the CD40 agonist is an agonistic CD40 antibody.